PATENT COOPERATION TF ATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/016614	15.06.2004	20.06.2003

International Patent Classification (IPC) or both national classification and IPC
C12N15/86, C12N5/10, C12N7/01, C07K14/075, A61K39/235, A61K48/00, C12N15/34

Applicant
THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Brenz Verca, S

Telephone No. +49 89 2399-7702

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/016614

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 20-43

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 20-43

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-19

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-19
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item IV

Lack of unity of invention

This Authority considers that there are 53 inventions covered by the claims indicated as follows:

Invention 1:
Claims 1-19
Subject: Chimeric adenovirus comprising ITRs, E1a, E1b and E4 from a first adenovirus and an internal region comprising genes encoding penton,hexon and fiber from a second adenovirus; host cell comprising said chimeric adenovirus; method of generating said chimeric adenovirus; method of culturing a chimeric adenovirus comprising ITRs from a first adenovirus and an internal region comprising genes encoding penton,hexon and fiber from a second adenovirus.

Invention 2:
Claim 20
Subject: Simian adenovirus 18 (SA18) genomic sequence of SEQ ID No: 12 or complementary nucleic acids.

Inventions 3-53:
Claims 21-43(all partially)
Subjects: Nucleic acid consisting of the corresponding SA18 region listed in claim 21; protein encoded by said nucleic acid; composition comprising a capsid protein where this applies; nucleic acid molecule comprising a said region as heterologous sequence; pharmaceutical composition comprising said nucleic acid molecule; recombinant adenovirus comprising a protein selected from hexon, penton, fiber from SA18; host cell comprising a heterologous nucleic acid comprising said nucleic acid; host cell expressing gene products from said region; composition comprising said recombinant virus; method for delivering a heterologous gene; method for repeat administration of a heterologous gene; method for producing a selected gene product; method for eliciting an immune response;

where the each of the corresponding SA18 (SEQ ID No. 12) regions listed in claim 21 and, where applying, claims referring thereto represents a separate

invention, namely:

invention 3: 5' inverted terminal repeat (ITR)
invention 4: E1a region
invention 5: E1a 13S region
invention 6: E1a 12S region
invention 7: E1a 9S region
invention 8: E1b region
invention 9: small T region
invention 10: large T region
invention 11: protein IX region
invention 12: protein IVa2 region
invention 13: E2b region
invention 14: L1 region
invention 15: 28.1 kD protein region
invention 16: polymerase region
invention 17: agnoprotein region
invention 18: 52/55 kD protein region
invention 19: protein IIIa region
invention 20: L2 region
invention 21: penton region
invention 22: protein VII region
invention 23: protein VI region
invention 24: protein Mu region
invention 25: L3 region
invention 26: hexon protein region
invention 27: endoprotease region
invention 28: 2a protein region
invention 29: L4 region
invention 30: 100 kD protein region
invention 31: 33 kD protein homolog region
invention 32: protein VIII region
invention 33: E3 region
invention 34: E3 ORF1 region
invention 35: E3 ORF2 region
invention 36: E3 ORF3 region
invention 37: E3 ORF4 region
invention 38: E3 ORF5 region
invention 39: E3 ORF6 region
invention 40: E3 ORF7 region
invention 41: E3 ORF8 region
invention 42: E3 ORF9 region
invention 43: L5 region
invention 44: fiber protein region
invention 45: E4 region
invention 46: E4 ORF1 region
invention 47: E4 ORF2 region
invention 48: E4 ORF3 region
invention 49: E4 ORF4 region
invention 50: E4 ORF5 region
invention 51: E4 ORF6 region
invention 52: E4 ORF7 region
invention 53: 3'-ITR

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The problem to be solved by invention 1 is the provision of methods and means for the growth to high titre of adenoviruses that are difficult to grow at high yield, as well as to increase their antigenic dissimilarity (description p. 50, lines 3-15).
The solution is the chimeric adenovirus of independent claims 12 and 13 and the methods of independent claims 1 and 11. The special technical feature common to the independent

claims of invention 1 is a chimeric adenovirus comprising at least the inverted terminal repeats of a first adenovirus serotype and an internal region comprising at least the genes encoding penton, hexon and fiber from a second, different adenovirus serotype.

With regard to invention 2, the closest prior art is considered to be WO03046124 (5 June 2003), disclosing the nucleotide sequence of 6 simian adenoviruses useful for the production of recombinant viral vectors and vaccines. The problem to be solved by invention 2 is thus the provision of the genomic sequences of a further simian adenovirus with the same intended uses. The solution is the nucleic acid sequence of SEQ ID No: 12, corresponding to the complete genomic sequence of simian adenovirus 18 (SA18).

It is immediately apparent that said inventions solve different problems and that the corresponding solutions also do not share any common special technical feature in the sense of Rule 13.2 PCT, thus a lack of unity exists a priori between invention 1 and invention 2.

In addition, the nucleic acids of claim 21 corresponding to single SA18 regions are considered to constitute single inventions for the following reasons:

Although the subject-matter relates to the genome of a single virus (SA18 of invention 2) and the claimed regions (inventions 3-53) are the product derived from that genome, a priori this feature can not be regarded as a special technical feature representing a single novel and inventive concept. The mere fact that polynucleotides are derived from the same source is indeed not sufficient to meet the criteria for unity of the invention (Rule 13 PCT, PCT Guidelines 10.52). In the case where the claimed regions encode a protein, said proteins exhibit different structural and functional properties (compare e.g. a polymerase and a capsid protein). Therefore, due to the lack of any structural AND functional relationship, there is no special technical feature linking the different regions claimed, contrary to the requirements of Rule 13 PCT.

Apart from this non-unity a priori, it is considered that a lack of unity objection exists also on the basis of an alternative reasoning taking into consideration that the concept common to the claimed SA18 regions is that said regions are nucleic acids from simian adenovirus 18. However, simian adenovirus 18 was commercially available before the filing of the application (ATCC catalogue number VR-943) and routine techniques for obtaining nucleic acid

sequences, including the entire genomic sequence of an adenovirus were available to the skilled person, as exemplified by Farina et al in J.Virology 75:11603 (2001) for chimpanzee adenovirus C68, also purchased from ATCC and sequenced by a commercial supplier (Farina et al. see Materials & Methods section). Consequently, said concept is not inventive and there is a lack of unity.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 00/03029 A (INTROGENE BV) 20 January 2000 (2000-01-20)

D2: YOUIL RIMA ET AL: "Hexon gene switch strategy for the generation of chimeric recombinant adenovirus" HUMAN GENE THERAPY, vol. 13, no. 2, 20 January 2002 (2002-01-20), pages 311-320, ISSN: 1043-0342

D3: WU HONGJU ET AL: "Construction and characterization of adenovirus serotype 5 packaged by serotype 3 hexon." JOURNAL OF VIROLOGY, vol. 76, no. 24, December 2002 (2002-12), pages 12775-12782, XP002301538 ISSN: 0022-538X

D4: WO 03/046124 A (TRUSTEES OF THE UNIVERSITY OF ; GAO GUANGPING (US); ROY SOUMITRA (US);) 5 June 2003 (2003-06-05)

D5: FARINA S F ET AL: "Replication-defective vector based on a Chimpanzee adenovirus" JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 75, no. 23, December 2001 (2001-12), pages 11603-11613, ISSN: 0022-538X

D6: STEVENS D.: "American Type Culture Collection Catalogue of strains II: Viruses and antisera" 1983, AMERICAN TYPE CULTURE COLLECTION, ROCKVILLE MARYLAND

D7: ROY SOUMITRA ET AL: "Characterization of a family of chimpanzee adenoviruses and development of molecular clones for gene transfer vectors" HUMAN GENE THERAPY, vol. 15, no. 5, May 2004 (2004-05), pages 519-530, XP002301507 ISSN: 1043-0342

As mentioned under section IV, the feature common to the independent claims of invention 1 is a chimeric adenovirus comprising at least the inverted terminal repeats (ITRs) of a first adenovirus serotype and an internal region comprising at least the genes encoding penton, hexon and fiber from a second, different adenovirus serotype.

This combination of technical features is neither disclosed nor suggested in any of D1-D7 taken alone or in combination, therefore the requirements of novelty of Article 33(2) PCT) and inventive step of Article 33(3) PCT are fulfilled.

Claims 1-19 also appear to be industrially applicable as required by Article 33(4) PCT.

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